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Clinical Implications of Microarray in Cancer Medicine

Jiun Kang

Department of Biomedical Laboratory Science, Ssangyong-dong 456, Seobuk-gu, Cheonan, Chungnam, 330-718, South Korea

ABSTRACT

Cancers are associated with an array of orchestrated genetic changes and the identification of changes causally related to the carcinogenic process. To elucidate the mechanism of cancer carcinogenesis, it is necessary to reconstruct molecular events at each level. Microarray technology is a versatile platform that allows rapid genetic analysis to take place on a genome-wide scale and has revolutionized to evaluate genetic markers and changes in cancer genetics. Since their development in the mid-1990s, these technologies have become a key tool in the fight against cancer. Microarray data have led to the identification of molecular subclasses of solid tumors characterized by distinct oncogenic pathways, as well as the development of multigene prognostic or predictive models equivalent or superior to those of established clinical parameters. Currently, several genomic aberrations discovered by these assays are presently being used as predictive markers for cancer treatment with targeted therapeutics. But how do microarrays work and just how have they been used in cancer diagnosis and treatment thus far? Here, we presented a summary of the main applications of microarrays in the field of targeted therapies of cancer and discussed their potential in clinical implementation.

Key words: Microarray technology, genomic aberration, predictive biomarker, targeted therapeutics, cancer medicine

INTRODUCTION

Microarray technology is a versatile platform that allows application of rapid genetic analysis on a genome-wide scale (Nambiar *et al.*, 2008). It increases the possibilities both for the analysis of gene expression and for monitoring of genetic changes (Snijders *et al.*, 2000). The promise of this technology is that assessment of a combination of genes will be more predictive of clinical outcome including; response to therapy than any single gene alone (Andre and Puztai, 2006). Recent discoveries of genomic alterations underlying and promoting the malignant phenotype, together with an expanded repertoire of targeted agents, have provided many opportunities to conduct hypothesis-driven clinical trials (Dienstmann *et al.*, 2013).

In the field of molecular-targeted therapy for cancer, these methodologies have enabled the identification of molecular targets with “key” roles in neoplastic transformation or tumor progression and the subsequent development of targeted agents, which are most likely to be active in a specific molecular setting (Sanoudou *et al.*, 2012). Moreover, the ability to profile each unique cancer for actionable aberrations by using this technologies in a cost-effective way provides unprecedented opportunities for using matched therapies in a selected patient population. Consequently, DNA microarray technologies will undoubtedly prove to be a key technology leading to better cancer classification, prognosis and outcome prediction. But how do micro arrays work and just how have they been used in cancer diagnosis and treatment thus far?

Here, we present an overview of the clinical value of microarray technologies in clinical oncology, focusing on the efficacy assessment, including identifying novel therapeutic targets, discovering molecular markers that predict response to therapy and predictive factors for the therapy outcome.

Turning into the genetic orchestra using micro arrays in cancer medicine: Cancer is a genetic disease of somatic cells arising from accumulation of genetic changes and from the abnormalities of suppressor genes and oncogenes that are frequently associated with carcinogenesis (Ramaswamy and Golub, 2002). Accordingly, a major focus in cancer research is on identifying genetic markers that can be used for precise diagnosis or therapy (Sriram *et al.*, 2011).

Basis for predicting prognosis for the different types of cancer: Over the past decade, microarray technologies have been used by translational scientists to break down the complexity of cancer genome for better categorization based on oncogenic and treatment-resistance pathways (Bouchalova *et al.*, 2010). This technologies can be defined as an ordered collection of microspots (the probes), each spot containing a single species of a nucleic acid and representing the genes of interest (Russo *et al.*, 2003). Hybridization is performed using corresponding probes that recognize and attach to the solid support; these can be complementary DNAs (cDNAs), oligonucleotides of varying length, or genomic sequences that are either radioactively or fluorescently labeled. An array containing thousands of spots immobilized at predetermined locations can be generated by applying the DNA to the array using pins or inkjet technology, or by *in situ* photolithographic synthesis of oligonucleotides (Abdullah-Sayani *et al.*, 2006). Figure 1 represents block diagram of the microarray life cycle. Shown are the 4 steps of microarray experimentation.

Many studies have identified gene-signatures or a group of genes that could be used as prognostic and treatment-predictive markers of cancer. There are over 5,000 publications currently available on PubMed about prognostic and treatment-predictive markers in cancer identified using microarray (Thangaraj *et al.*, 2013). Several genomic aberrations were discovered by these methodologies that are now used as predictive genetic markers for treatment with targeted therapeutics. In the study of malignant peripheral nerve sheath tumors (MPNSTs), Yang and Du (2013) reported that the genomic and molecular aberrations of EGFR, IGF1R, SOX9, EYA4, TOP2A, ETV4 and BIRC5 genes exhibit great promise as personalized therapeutic targets

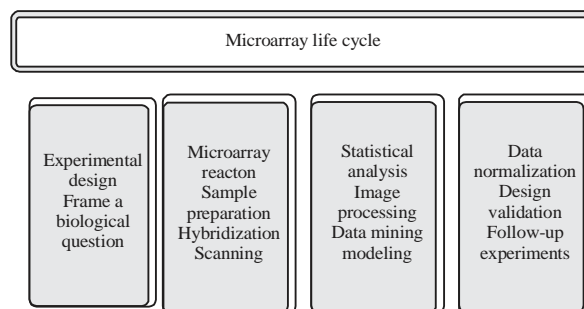


Fig. 1: Block diagram of the microarray life cycle. Shown are the 4 steps of microarray experimentation: Step 1: Study design, Step 2: Microarray reaction, Step 3: Statistical analysis and Step 4: Data normalization

for MPNST patients. Furthermore, Uchida *et al.* (2011) described that copy number loss at 3p26.3 including the CHL1 (cell adhesion molecule with homology to L1CAM1) gene is a novel potential marker for predicting the prognosis of patients with oral squamous cell carcinoma. In a similar study, a low-level gain of the 12q24.31 was identified as a potential new biomarker for neuroblastoma progression (Wolf *et al.*, 2010).

Moreover, Zhu *et al.* (2010) used gene expression profiling on 62 non-small cell lung cancers (NSCLCs), who were in the observation group of the National Cancer Institute of Canada Clinical Trials JBR.10. From the data obtained, they identified a 15-prognostic gene signature. Interestingly, the gene signature was also predictive of response to adjuvant chemotherapy in a cohort of 71 patients. Importantly, this is one of the first studies to identify a gene signature that is both prognostic and predictive.

Another study of gene expression analysis, Ramaswamy *et al.* (2002) compared 12 metastatic adenocarcinoma nodules of diverse origin (lung, breast, prostate, colorectal, uterus and ovary) with 64 primary adenocarcinomas representing the same tumor types from different individuals to form a training set of 76 samples. They found 128 genes that were differentially expressed between the metastatic and the primary tumors and used these genes to build a predictor that was then tested to classify primary tumors of different origins.

Roepman *et al.* (2005) were also able to build a gene predictor that could detect local lymph node metastases from primary head and neck squamous cell carcinomas (HNSCCs). The predictor, formed by 102 genes, outperformed current clinical diagnostic methods with an overall predictive accuracy of 86% while the current diagnostic method had 68%. This improvement in the diagnosis has a lot of relevance for treatment selection and the authors estimated that by using micro arrays to diagnose the existence of local metastases, 75% patient that were really metastasis free but diagnosed as carrying possible metastases, could have avoided radical neck dissection treatment. This work also presents interesting biological information about the genes differentially expressed between the two classes of primary tumors compared here: those with local metastases and those without local metastases. Interestingly, half of the 102 genes that formed the predictor have unknown role in metastases formation and could give insights into how this process occurs.

A large number of markers also identified by micro arrays are non-invasive, using body fluids like blood or saliva for the test. Li *et al.* (2004) demonstrated the utility of salivary transcriptome diagnostics by microarray to detect oral cancer. They identified potential salivary biomarkers namely, IL8, IL1B, DUSP1, HA3, OAZ1, S100P and SAT that can distinguish oral squamous cell carcinoma with high sensitivity (91%) and specificity (91%).

In the hematological field, micro arrays have contributed to an increasingly well-defined molecular taxonomy of leukemias and lymphomas. This has led to the segregation of morphologically identical tumors according to molecular patterns predictive of distinct clinical outcomes (Gabriele *et al.*, 2006; Song *et al.*, 2006; Tagliafico *et al.*, 2006; Pospisilova *et al.*, 2012; Oscier *et al.*, 2010; Gonzalez *et al.*, 2013; Bullinger *et al.*, 2004; Perez-Diez *et al.*, 2007; Alizadeh *et al.*, 2000). Moreover, gene expression studies led to the discovery of new hematological disease subclasses characterized by unique molecular profiles suggesting the development of diagnostic strategies based solely on gene expression profiling (Gabriele *et al.*, 2006).

For instance, using a cohort of 76 Acute Myeloid Leukemia (AML) patients, one study was able to identify gene expression changes that correlated with response to chemotherapy and thus was predictive of chemo sensitivity (Song *et al.*, 2006). In a similar manner, Tagliafico *et al.* (2006) used gene expression analysis to determine a molecular signature that is predictive for sensitivity to

induction of differentiation by retinoid. Another important aspect of molecular diagnostics is the analysis of prognostic markers in Chronic Lymphocytic Leukemia (CLL) (including TP53 mutations, IGHV mutation and CLLU1 expression) (Pospisilova *et al.*, 2012; Oscier *et al.*, 2010; Gonzalez *et al.*, 2013).

Furthermore, Bullinger *et al.* (2004) made a larger scale study on 116 samples from adults with AML including 45 with normal karyotype. Even though karyotype abnormalities are the most powerful prognostic factor in AML patients, 35-50% of patients showing a normal karyotype have an unpredictable prognosis. Class discovery analysis of all the AML samples divided them into new molecular subclasses. Interestingly, the 45 patients with normal karyotype were divided in two groups that were found to have different survival rates. The authors then built a 133 genes predictor that was able to differentiate among patients with normal karyotype into good and poor prognosis. This study was the first one able to do so in AML discovery of new subtypes of AML, the complementary clinical information on survival rates allowed the additional prognostic value to the new AML classification (Perez-Diez *et al.*, 2007).

Furthermore, in the study of large B-cell lymphoma (DLBCL) (Alizadeh *et al.*, 2000), the authors distinguished two previously unknown groups of DLBCL “germinal center B-like DLBCL” and “activated B-like DLBCL” named so because of the main differences between the genes involved in B-cell activation and germinal center formation. These two new taxonomic groups have not only biological relevance but also an important prognostic value, because 5 years after the anthracycline-based chemotherapy treatment, 76% of the germinal center B-like DLBCL patients survived, while only 16% of activated B-like DLBCL survived (Ramaswamy *et al.*, 2002). Figure 2 shows the schematic overview of the applications of microarray technologies in cancer medicine.

Application of micro arrays in personalized therapeutics for the different types of cancer: More importantly, these prognostic and treatment-predictive markers and their associated

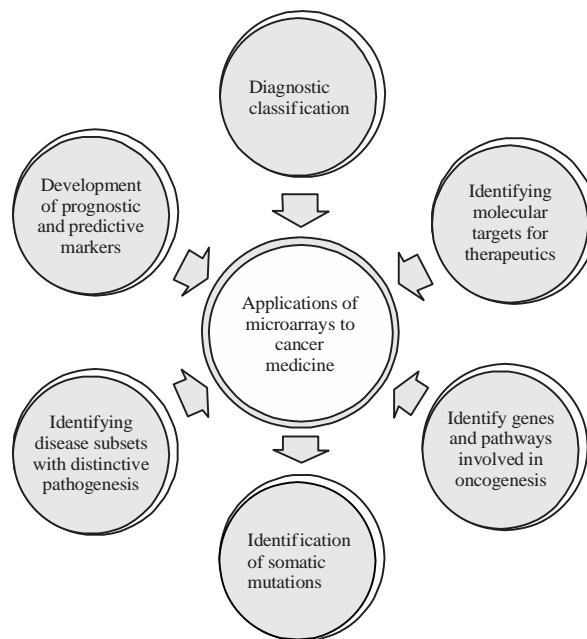


Fig. 2: Schematic overview of the applications of microarray technologies in cancer medicine

pathways could be potential therapeutic targets. In the study of pediatric AML, FLT3 mutations were found in nearly 20% of the patients (Meshinchi *et al.*, 2006) and Fli/Internal Tandem Duplication (ITD) was found to constitutively activate the FLT3 receptor tyrosine kinase to cause autonomous, cytokine-independent proliferation *in vitro*. A few FLT3-inhibitors, such as; PKC412 (Stone *et al.*, 2005) are currently being tested in clinical trials in adults and they have shown great potential in the treatment of pediatric AML. This is the case for the drug tipifarnib, a farnesyl transferase inhibitor originally developed to target oncogenic RAS and shown to be effective in treatment of refractory and relapsed acute leukemias. One study identified genes and genetic pathways that respond to treatment with tipifarnib and revealed the presence of additional targets in the cell, in addition to RAS (Raponi *et al.*, 2004). Such analysis includes SS18-SSX fusions in synovial sarcomas, EWSR1 fusions in Ewing's sarcoma and PAX3/7-FKHR fusions in alveolar rhabdomyosarcomas (Thway *et al.*, 2010). These are only a selected number of studies that serve as examples of the potential use of microarray technologies in oncology medicine. The expectations from applications of these methodologies in clinical oncology are high because their utilization in clinical practice can markedly improve our current strategies for cancer diagnosis and prediction of the clinical outcomes. This in turn may lead to the identification of treatments that are optimized according to the genetic background of individual patients and the biological characteristics of their tumors.

In 2004, the U.S. Food and Drug Administration (FDA) recognized the importance of genetic data, such as microarray data, for the development of new drugs and the FDA began to receive attached data when new drug applications were submitted. The first and the most prominent example of a predictive genomic aberration in cancer applies to Chronic Myelogenous Leukemia (CML); the discovery (1960) and description (1973) of the Philadelphia chromosome, a reciprocal translocation between chromosome 9 and 22, led to the development of the molecular-targeted tyrosine kinase inhibitor (TKIs) STI571 (Gleevec; Novartis, East Hanover, NJ) for the treatment of this disease (Druker *et al.*, 2001a, b). This exemplary case is regarded as a milestone in personalized medicine.

The first pharmacogenetic microarray test was approved by the FDA in 2005 and was manufactured by Roche. This test classifies patients according to their Single Nucleotide Polymorphisms (SNPs) profiles of the cytochrome P450 (CYP) genes CYP2D6 and CYP2C19 as poor, intermediate, extensive or ultra rapid metabolizers. This information is then used by the clinicians to adapt the dose specifically for therapeutics that are metabolized by these two enzymes (Tan and Du, 2012).

With the emergence of two anti-Epidermal Growth Factor Receptor (EGFR)-targeted antibodies cetuximab (Erbix) and panitumumab (Vectibix) the treatment of metastatic colorectal cancer (CRC) has also entered the era of personalized treatment. Of these two antibodies, one is a human-mouse chimeric IgG1 monoclonal that was approved by FDA as a second-line treatment of CRC and the other is a human IgG2 k monoclonal antibody that was approved by the FDA as a third-line treatment drug (Smeets *et al.*, 2006).

Major advances have also been made in lung cancers for novel-targeted therapeutics. The most recent example is that of the approval of crizotinib, a small-molecule dual inhibitor against the kinases of the proteins MET and ALK. This inhibitor has been approved for patients whose tumors harbor an ALK rearrangement (chiefly EML4-ALK fusion). Furthermore, in advanced Non-Small Cell Lung Cancer (NSCLC) patients, EGFR TKIs have demonstrated clinical efficacy. Patients whose tumors harbor EGFR somatic mutations have a 70% response rate to TKIs as compared with 10% for patients with wild-type EGFR (Perez-Soler, 2009).

Furthermore, in the study of breast cancers, Ramaswamy *et al.* (2002) described that progress along different genomic pathways (HER2, cyclin D and 8q and 20q amplifiers) and allow the identification of novel breast cancer oncogenes within complex amplicons (Smeets *et al.*, 2006). Specifically, oncogenes that are linked with poor prognosis are more likely to provide new information on cancer progression. For instance, amplification of the HER2 gene (Vanden *et al.*, 2007) in breast cancers is associated with poor prognosis in patients with early stage and metastatic breast cancer. Trastuzumab is a humanized monoclonal antibody directed against the HER2 protein, which, as a consequence of the above mentioned amplification, is over expressed in approximately 25% of patients with primary invasive breast cancer (Calasanz and Cigudosa, 2008). This antibody was later modified and is now known as trastuzumab (Albertson and Pinkel, 2003) and in 2010, it was FDA approved in combination with letrozole for postmenopausal women with hormonal receptor positive and HER2+MBC (Midorikawa *et al.*, 2007).

In a similar study, increased expression of Mitotic Arrest Deficient-Like1 (MAD1L1) was found to be insensitive to taxol treatment in breast cancer (Sun *et al.*, 2013). Taxol being one of the most commonly used drug in breast cancer treatment, it will be useful to check a patient for MAD1L1 expression before administering the drug. A patient with high MAD1L1 could be suggested alternative treatment to avoid chemo resistance. Consequently, in the era of personalized cancer medicine, companion diagnostics have progressed to the front line of targeted prescription of therapeutics and have become a critical step in the pathological diagnosis of the abovementioned tumors.

These are only a selected number of studies that serve as examples of the potential use of microarray technologies in oncology medicine. The expectations from applications of these methodologies in clinical oncology are high because their utilization in clinical practice can markedly improve our current strategies for cancer diagnosis and prediction of the clinical outcomes. This in turn may lead to the identification of treatments that are optimized according to the genetic background of individual patients and the biological characteristics of their tumors. Furthermore, global sharing of the genomic and pathological data that are now accumulating in publicly available databases will aid in better understanding the genetic mechanisms and driving pathogenic abnormalities.

While current microarray technologies may be still be too expensive for routine applications, especially, when studying larger series of samples. Furthermore, several procedures need to be further optimized and validated prior to the implementation of micro arrays into routine clinical practice. These include; selection of optimal capture molecules, standardized hybridization protocols and standardized data collection and interpretation. In the future, with the introduction of massive whole-genome parallel sequencing, an even more complete map of the genomic changes present in malignant cells will be obtained. The cost of these technologies is probably then going to further decrease due to wider use and automation.

CONCLUSION

In this study, we presented an overview of the clinical value of microarray technologies in clinical oncology, discussed their current application, as well as outlined their potential applications in clinical oncology. Given its excellent performance in detecting predictive genetic biomarkers in clinical oncology, application of microarray technologies to cancer medicine could be a logical approach toward establishing a better management of cancer patients. Furthermore, the ongoing technical advancements and the growing databases of disease-specific profiles will enhance the

current cancer diagnosis, prognosis and treatment paradigms as well as assist physicians in delivering personalized treatment plans in order to minimize treatment-related toxicity and to improve prognosis.

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